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Case report

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Kluyvera ascorbata: An unusual cause of neonatal sepsis

Summary

Kluyvera ascorbata is a Gram-negative bacillus that rarely causes sepsis in the neonatal period, with few descriptions in the medical literature.

Objective: To report three cases of *Kluyvera ascobata* sepsis in newborns hospitalized in a neonatal intensive care unit (NICU). Clinical cases: three neonates aged 28, 34 and 37 weeks gestationally presented with late sepsis due to this microorganism. *Kluyvera ascobata* was identified in blood cultures in the three neonates, and was not isolated in cephallospinal fluid or urine in the three neonates. Newborns received contact isolation and parenteral meropenem for 7 days. One of them received a transfusion of platelets and red blood cells, while another patient received a transfusion of platelets. An outbreak of *Kluyvera ascobata* was declared in the NICU, and the action plan was executed, which included contact isolation, change of central vascular lines, antibiotic therapy for 7 days, an educational campaign on hand hygiene, and prevention packages in infections associated with devices to control their adherence. The evolution of the three neonates was favorable, with one of them being discharged home, while the other two remained hospitalized until the ideal weight gain was obtained for their discharge.

Conclusions: Three cases of neonatal sepsis due to *Kluyvera ascobata* in an outbreak occurring in a NICU that survive without compromise of other patients after treatment. It is the first time in 20 years that this NICU has been opened or that neonatal sepsis has been presented by this microorganism.

a) What is known about the subject of this study?

There are few publications on neonatal sepsis due to *Kluyvera ascobata*, a microorganism distributed in the environment, in soil and water. It is considered by many authors to be a normal commensal in the gastrointestinal, respiratory and urinary tracts of the human being.

b) What does this study contribute to what is already known?

Kluyvera ascobata is a commensal microorganism, which in immunocompromised situations can cause severe sepsis with neonatal mortality. Some reports report overall mortality rates that are close to 10%. *Kluyvera ascobata* sepsis is rare, but in recent years events have been reported in adults and children, so we can argue that *Kluyvera ascobata* is emerging as an unusual but significant microorganism of infections in adults and children.

Keywords: neonate, sepsis, late neonatal sepsis, *Kluyvera ascorbata*, neonatal intensive care unit

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Introduction

Bacteria of the genus Kluyvera are motile Gram-negative bacilli belonging to the family Enterobacteriaceae defined in 1936 by Kluyver and van Niel,[1] while its taxonomic location was confirmed by molecular methods in 1981.[2] It is found in the environment as a free-living microorganism in water, milk, soils and sewage, it has also been identified in hospital sinks and edible products of animal origin. It is part of the usual microbiota of the human digestive, respiratory and urinary tract, but is usually found in low concentrations.[3,4]

Although *Kluyvera ascobata* is recognized today as a rare cause of infections in adults and children,[5] there are some case reports describing *Kluyvera ascobata* causing urinary tract, bloodstream and abdominal infections, being reported as a cause of healthcare-associated infections, with overall mortality between 10-12%.[6]

This paper is presented to report the presence of three cases of neonatal sepsis within an outbreak in a NICU with a probable unidentified common source at the end of the events (parenteral nutrition cultures, negative dairy products for *Kluyvera ascobata* growth), with a good clinical evolution and no neonatal mortality.

Presentation of cases

Case 1

Early term neonate, daughter of an 18-year-old mother, pregnant 1 and childbirth 1. Well-controlled pregnancy. At birth, appropriate weight, height and head circumference for gestational age, with immediate abnormal adaptation due to the presence of respiratory distress with audible whining and subcostal retraction (Silverman Andersen 3/10), and he was hospitalized with a diagnosis of transient tachypnea. On admission, he was catheterized in the vein and umbilical artery, receiving non-invasive nasal ventilation in the form of continuous end-expiratory pressure (nasal CPAP) and a venous infusion of 10% dextrose. At 12 hours of age, parenteral and enteral nutrition was started. On the third day of life, parenteral nutrition, nasal CPAP and umbilical arterial catheters were withdrawn. At 70 hours of age, it presents clinical manifestations suggestive of neonatal

sepsis, which is why laboratory studies, microbiology and diagnostic images are taken (Table 1). The blood count was normal, and total and unconjugated bilirubin was normal. La proteína C-reactive was elevated, cerebrospinal fluid cytochemistry, urinalysis, Gram staining, and cerebrospinal fluid and urine were normal (Table 2).

Peripheral blood culture one was positive at 7 hours and 36 minutes of incubation, peripheral blood culture two was positive at 9 hours and 15 minutes of incubation, and catheter scan blood culture was positive at 2 hours and 15 minutes of incubation for *Kluyvera Ascorbata* (Table 3). Renal and urinary tract ultrasound identifies grade I left renal hydronephrosis. Chest x-ray showed no focal consolidation, pneumothorax, or effusion. Antimicrobial susceptibility is shown in Table 3. Treatment is performed for 7 days with intravenous meropenem, contact isolation for 3 days, and control blood culture at 72 hours of negative incubation for bacterial growth. The rest of the hospital stay passed without events or complications, with improvement in his clinical outcome, and he was discharged alive from the NICU with an outpatient follow-up order for pediatrics and nephrology.

Case 2

Moderate preterm infant, daughter of a 30-year-old mother, pregnant 1 and childbirth 1. Pregnancy was controlled from the 11th week of gestation with 3 prenatal check-ups. The patient was pregnant with gestational hypothyroidism since week 20 (treated with levothyroxine), spontaneous preterm labor, with incomplete intramuscular betamethasone maturation (a dose of betamethasone of 12 mg intramuscular close at birth), intrapartum antibiotic prophylaxis for *Streptococcus agalactiae* with ampicillin 2 g, magnesium sulfate from hospital admission, and a dose of cefazolin 30 minutes prior to cesarean section as intrapartum antibiotic prophylaxis. She was born via emergency cesarean section with weight, height, and head circumference appropriate for gestational age, with normal immediate adaptation. She was transferred to the neonatal NICU with non-invasive nasal ventilation such as continuous end-expiratory pressure (nasal CPAP), good respiratory effort, respiratory distress (Silverman Andersen 1/10) and 100% saturation. Furthermore, she was hospitalized with a diagnosis of moderate prematurity, hyaline membrane disease, and risk of early sepsis. On admission, she was catheterized in the vein and umbilical artery, continuing in nasal CPAP. A dose of intratracheal surfactant of 200 mg/kg was administered, along with intravenous ampicillin and amikacin, venous caffeine citrate and parenteral nutrition. Early sepsis was ruled out due to its favorable clinical evolution and negative blood culture for bacterial growth at 24, 48 and 72 hours of incubation. During the stay, he had significant hyperbilirubinemia, so he received conventional phototherapy. Due to the presence of persistent apneas, the dose of venous citrate caffeine is increased from 5 to 10 mg/kg/day. On the second day of life, enteral nutrition with breast milk was started at a dose of 30 cc/kg/day in 8 doses. On the fifth day of life, a transthoracic echocardiogram was performed, finding a restrictive patent ductus arteriosus with no hemodynamic repercussions, good biventricular function, no indirect signs of pulmonary hypertension, and no functional or structural heart disease. The umbilical arterial catheter was removed on the fifth day of life. At six days of age, a blood count was requested due to persistent apneas, which shows normal hemoglobin, a normal number of leukocytes and neutrophils, and low platelets (Table 1). With this result, it was decided to transfuse platelets at a dose of 10 cc/kg/dose, to take umbilical venous catheter blood cultures, two peripheral blood cultures, urine urinalysis and Gram, cytochemical, Gram and cerebrospinal fluid culture, and cefepime and venous amikacin were started (Table 2). The umbilical venous catheter was removed on the seventh day of life, and a percutaneous catheter was inserted into the upper extremity. On the eighth day of life, A second blood count is done with the presence of anemia, leukocytosis, neutrophilia and thrombocytopenia. It was decided to transfuse with compatible red blood cells at a dose of 15 ml/kg. On January 31, they reported isolation in the three blood cultures of *Kluyvera ascorbata* (Table 3), withdrawing cefepime and amikacin, and starting meropenem intravenously until completing 7 days of treatment. On the ninth day of life, a third blood count was obtained that reported normal hemoglobin, normal white blood cell count, and low platelets. The control blood culture at 72 hours of incubation was negative for bacterial growth. The rest of the hospital stay passed without events or complications, and apneas were controlled, maintaining caffeine citrate at a dose of 5 mg/kg enterally. The newborn is hospitalized to continue his weight gain and be discharged home.

Case 3

Moderate preterm newborn daughter of a 32-year-old mother, 6 pregnant women, 3 abortions, 2 births and 1 cesarean section. The pregnant woman had 6 prenatal check-ups from week 5, reporting a history of smoking until the beginning of the current pregnancy. In this pregnancy, she had spontaneous preterm labor in the third trimester, where she did not receive antenatal betamethasone for lung maturation, nor was screening for *Streptococcus agalactiae* performed, receiving adequate intrapartum antibiotic prophylaxis. She was born vaginally, with breech presentation with prolonged expulsion, head retention for 3 minutes, and perinatal asphyxia. Weight, height, and head circumference were adequate for gestational age. The Apgar score at 1-5-10-15 minutes was 4-5-5-5, requiring cardio-respiratory resuscitation for 6 minutes with bag-and-mask ventilation and chest compressions. She was then transferred to the NICU, where she was intubated and mechanically ventilated due to respiratory failure between the first and second days of life, subsequently continuing on non-invasive nasal ventilation until the third day of life. Upon admission, an umbilical venous catheter is inserted, a sample is taken for blood culture, which after 72 hours of incubation is negative for bacterial growth, and parenteral nutrition is started and administered until the sixth day of life. On the day of admission, ampicillin and venous amikacin were also started, which were suspended on the seventh day of life, when early neonatal sepsis was ruled out. Her evolution was satisfactory until the 5th day of hospitalization (108 hours of life), when she presented clinical deterioration with Clinical symptoms compatible with late neonatal sepsis (Table 1).

Table 1 Clinical characteristics in three neonates with *Kluyvera ascorbata sepsis*

Clinical Feature	Case 1	Case 2	Case 3
Age at admission (days)	0	0	0
Sex (M: male, F: female)	F	F	F
Gestational age (weeks)	37	28 + 6/7	34 + 6/7
Birth route (V: vaginal, C: cesarean)	V	C	V
Birth weight: grams (percentile)	2,680 (37.45)	1,340 (81.99)	2060 (21.33)
Height at birth: cm (percentile)	46.5 (31.69)	39 cm (65.59)	48 (93.15)

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Table 1 Continued.....

Clinical Feature	Case 1	Case 2	Case 3
Head circumference at birth cm (percentile)	33.5 (77.5)	27 (64.94)	31 (32.47)
Age of onset of infectious symptoms	70 hours	6 days	108 hours
Clinical manifestations of neonatal sepsis	Poor general clinical appearance, jaundiced skin coloration, tachycardia (heart rates greater tan 190/ minute), tachypnea, increased respiratory distress with constant respiratory whine, subcostal retraction and intercostal retraction (Silverman Andersen of 4/10) and yellow upper respiratory secretions.	Persistent apneas	Fever 38°C, marked jaundice, complaining and underactive.
Antibiotic treatment	Meropenem for 7 days		
Condition at discharge	Alive		

Laboratories are performed with elevated C-reactive protein, a blood count with mild anemia, a normal number of leukocytes and neutrophils, and a low number of platelets. Cytochemical and Gram cerebrospinal fluid were normal. Urinalysis and urine gram were normal. Normal serum sodium, potassium, and chlorine, and elevation of ionized calcium (Table 2). Three samples were also taken for two peripheral blood cultures and one central one, a sample for urine culture and cerebrospinal fluid culture. A venous umbilical catheter was removed, and epicutaneous catheter was inserted in the upper extremity. The neonate is isolated from contact, platelets are transfused, amikacin and cefepime are started, and they are withdrawn when blood cultures are reported as positive for bacterial growths at 7 hours of incubation, identifying the growth of *Kluyvera ascorbata* (Table 3). *Venous* meropenem was started and administered for 7 days. Her evolution is favorable, with clinical recovery, and the control blood culture at 72 hours of incubation was negative for bacterial growth. The rest of the hospital stay passed without events or complications, and he was hospitalized to continue his weight gain Percentil 81.99.

Table 2 Laboratories and microbiology in three neonates with sepsis due *to Kluyvera ascorbata*

Clinical Feature	Case 1	Case 2	Case 3
		Cbc 1	
Hemoglobin g/dl		12.2	
Hematocrit %		31.7	
Leukocytes /mm^3		5,110	
Neutrophils /mm^3		2,400	
Lymphocytes /mm^3		750	
Monocytes /mm^3		660	
Platelet count /mm^3		21,000	
		Cbc 2	
Hemoglobin g/dl	13.3	8.5	11.5
Hematocrit %	39	24.4	32.6
Leukocytes /mm^3	19,690	19,81	8,320
Neutrophils /mm^3	16,890	12,780	5,160
Lymphocytes /mm^3	830	3,760	12,680
Monocytes /mm^3	1,240	2,770	150
Platelet count /mm^3	91,000	57,000	16,000
		Cbs 3	
Hemoglobin g/dl		16.1 g/dl	
Hematocrit %		43.0%	
Leukocytes /mm^3		13,270	
Neutrophils /mm^3		8,270	
Lymphocytes /mm^3		2,710	
Monocytes /mm^3		2,000	
Platelet count /mm^3		83,000	
C-reactive protein mg/l (reference range 0-5 mg/l)	108.02	Not performed	129.6

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Table 2 Continued.....

Clinical Feature	Case 1	Case 2	Case 3
	Cerebrospinal fluid cytochemistry		
	Clear	Clear	Clear
pH	8.0	8.5	8.0
Density	1,020	1,020	1,020
Protein mg/dl	84.02	155.53	75.29
glucose mg/dl	88	63.1	491
Ldh U/l	116	66	81
Leukocyte count	0/mm^3	0/mm^3	0/mm^3
Gram stain and Indian ink stain:	negative for bacteria	negative for bacteria	negative for bacteria
	Urinalysis		
Density	1,020	1,015	1,030
pH	5.5	6.0	5.0
Leukocytes	0/µl	0/µl	0/µl
Protein mg/dl	50	100	78
Glucose mg/dl	80	100	56
Leukocytes /field Bacteriuria	0	2-5	2-5
Nitrites	negative	negative	negative
Leukocyte stearase	negative	negative	negative
Urine Gram stain	negative	negative	negative
	negative	negative	negative
Cerebrospinal fluid Culture for bacterial	negative	negative	negative
Urine culture	negative	negative	negative
Blood cultures	Peripheral (2) and central catheter (1): *Kluyvera ascorbata*	Peripheral (2): *Kluyvera ascorbata*	Peripheral (2) and central catheter (1): *Kluyvera ascorbata*
Other laboratories	Total bilirubin 12.64 mg/dl and indirect bilirubin 12.13 mg/dl	Chlorine 103.3 mmol/l, sodium 130 mmol/l, potassium 3.95 mmol/l; and ionized calcium 1.53 mmol/l (normal value 1.3 mmol/l)	

Table 3 Antimicrobial susceptibility of the three strains of *Kluyvera ascorbata*

Antimicrobial agent	Case 1		Case 2		Case 3	
	MIC	(µg/mL) - As	MIC	(µg/mL) - As	MIC	(µg/mL) - As
Ampicillin/sulbactam	≤8/4	S	≤8/4	S	≤8/4	S
Amikacin	≤8	S	≤8	S	≤8	S
Amoxicillin/Clavulanic acid	≤8/4	S	≤8/4	S	≤8/4	S
Ampicillin	≤8	R	≤8	R	≤8	R
Aztreonam	8	I	≤4	S	≤4	S
Ceftriaxone	≤1	S	≤1	S	≤1	S
Ceftazidime	≤1	S	≤1	S	≤1	S
Cefoxitin	≤8	S	≤8	S	≤8	S
Cefazolin	4	I	16	R	4	I
Cefepime	≤2	S	≤2	S	≤2	S
Cefuroxime	≤8	S	≤8	S	≤8	S
Ciprofloxacin	≤0.06	S	≤0.06	S	≤0.06	S
Ertapenem	≤0.5	S	≤0.5	S	≤0.5	S
Meropenem	≤0.5	S	≤0.5	S	≤0.5	S
Tazobactam/piperacillin	≤16	S	≤16	S	≤16	S
Trimetoprim/sulfametoxazol	≤2/38	S	≤2/38	S	≤2/38	S

S, susceptible; R, resistant; I, intermediate; MIC, minimum inhibitory concentration; As, Antimicrobial susceptibility

Discussion

The genus Kluyvera has four species: *Kluyvera cryocrescens*, *Kluyvera ascorbata*, *Kluyvera georgiana,* and *Kluyvera cochleae*, of which the first three have been isolated from humans, although infections by this microorganism are rare. They have the ability to invade multiple organs and have a tendency to form abscesses. It is still unknown whether *Kluyvera ascobata* infections are of endogenous origin, acquired from the environment, or both. These genus of microorganisms have the lipopolysaccharide of the wall and surface antigens that give them pathogenic power.[3,7] *Kluyvera ascobata* is associated with even severe infections in immunocompromised patients like our three cases, and has been reported as an associated cause of mortality.

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It has been linked to healthcare-associated infections, in outbreaks, and during the administration of medications such as heparin. *Kluyvera* spp, although rarely isolated in the laboratory, can be responsible for serious healthcare-associated infections, acquire numerous antibiotic resistance genes (ESBLs, etc.), and be the cause of outbreaks and epidemics.[8] It constitutes a reservoir of the CTX-M ESBL gene that can be mobilized by plasmids at the origin of resistance transfers to enterobacteriaceae such as *Escherichia coli*, a microorganism in which it manifests as an extended-spectrum β-lactamase (CTX-M type). In addition, only compliance with hygiene standards in hospital practice can limit its spread.[9,10] The case of *multidrug-resistant Kluyvera ascobata* has been documented,[11] as has resistance to carbapenems in *K. georgiana* strains carrying KPC-2.[12]

In this report, we describe an outbreak in a NICU with three cases of *Kluyvera ascobata* sepsis, neonates who were not mechanically ventilated, but with central catheters, with enteral nutrition and who had previously received or were receiving parenteral nutrition. The outbreak occurred within one day of each other in all three cases. The isolated *Kluyvera ascobata* strains showed the susceptibility patterns in the antibiogram described in Table 1.

In the literature, a case of a premature newborn similar to one of ours with late sepsis due to *Kluyvera ascobata* is described, who dies despite therapy with meronem.[13] Bolat F et al.,[14] Another case of neonatal sepsis is reported in an 8-day-old newborn without urinary or meningeal involvement like ours, with a clinical evolution after common meropenem treatment.

Newborns are more susceptible to sepsis, especially when they are premature, especially the most extreme due to exposures within a NICU and the immaturity of their immune system.[15] Ochi et al.,[16] reported sepsis and urinary tract infection in a newborn at term of 19 days who was treated for 10 days with cefotaxime with good clinical evolution. Karadağ et al.,[5] reported a case reported in a 19-day-old newborn woman who consulted for fever, irritability, lethargy, poor diet, tachycardia and tachypnea and diagnosed urinary tract infection and sepsis. He received antibiotic treatment for 10 days with cefotaxime with complete recovery.

Kluyvera ascobata strains in our neonates were resistant to first-generation cephalosporins and sensitive to ampicillin, ampicillin/sulbactam, third- and fourth-generation cephalosporins, and carbapenems. Kluyvera species are usually sensitive to the third-generation cephalosporins, amikacin, imipenem, aminoglycoside, aztreonam, fluoroquinolones, and tetracycline. More recently, these microorganisms have shown a tendency to increase resistance to commonly used antibiotics, which is mediated by the production of β-lactamases due to their ability to transfer genes encoding CTX-M-type extended-spectrum β-lactamases to other Enterobacteriaceae, resulting in the reduction of effective options for treating infections caused by these microorganisms.[17,18] Our patients were treated for 7 days with venous meropenem with negative control blood culture for the growth of this bacterium.

Conclusion

Kluyvera ascobata has been associated with clinically significant infections in neonates, such as urinary tract infection, bacteremia, and severe sepsis, as occurred in this NICU outbreak. In cases of neonatal sepsis, pediatricians and neonatologists should be aware of the potential for *Kluyvera ascobata* disease and initiate treatment early with the most effective antibiotics based on culture and susceptibility testing.

Ethical responsibilities

Protection of people and animals: The authors declare that the procedures followed conformed to the ethical standards of the committee of responsible human experimentation and in accordance with Resolution Number 8430 of 1993 of the Ministry of Health of the Republic of Colombia, with the World Medical Association and the Declaration of Helsinki.

Data confidentiality

The authors state that they have followed their workplace's protocols on the publication of patient data.

Right to privacy and informed consent

This study has been approved by the corresponding Research Ethics Committee, which according to the characteristics of the study has exempted the use of Informed Consent.

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Conflict of interest

The authors declare that they have no conflict of interest.

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